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(54) Pharmaceutical compositions for oral administration containing a gastroresistant coating based on acrylic polymers

(57) Pharmaceutical compositions for oral administration in tablet form, containing mesalazine or pharmaceutically acceptable salts thereof as the active ingredient useful for the treatment of inflammatory or irritative intestinal diseases, comprising:

a) a nucleus comprising the active ingredient, and
b) a filming coating comprising a methacrylic acid/methyl acrylate/methyl methacrylate terpolymer, completely insoluble at pH ≤6.0 and completely soluble at pH >7.0, allowing the release of the active ingredient only in the terminal portion of the intestine.

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Description

Field of the invention

[0001] The present invention relates to pharmaceutical compositions, based on mesalazine or pharmaceutically acceptable salts thereof, to be administered by the oral way in tablet form, comprising a gastroresistant coating and being useful for the treatment of inflammatory or irritative intestinal diseases.

State of the art

[0002] There are a number of active ingredients efficacious in intestinal diseases, which however, cannot be administered *per os*, as they are inactivated before reaching the intestine. Furthermore, should said substances cause gastric intolerance and ulceration, their transit through the stomach produces untoward side effects.

[0003] For example, mesalazine, i.e. 5-aminosalicylic acid, is a well known drug effective in the treatment of inflammatory intestinal diseases, in particular ulcerative colitis and Crohn's disease, which, however, cannot be administered by the oral way, being absorbed and inactivated before reaching the terminal portion of the intestine, where inflamed and irritated zones are concentrated.

[0004] This is one reason why a number of compositions suitable for rectal administration have been developed, whose active ingredients directly act on the mucous membrane of the colon, without being degraded in the stomach. However, patients find the use of said formulations somehow uncomfortable and less acceptable than oral formulations. Moreover, the colon right side cannot be reached and efficaciously treated by rectal formulations.

[0005] Alternatively, investigations have been conducted on formulations suitable for oral administration, providing a delayed release of the active ingredient directly in the intestine.

[0006] Exemplary preparations of this type are described in European Patent Application No. EP 366,621 (Istituto De Angeli SpA). The pharmaceutical composition of this patent application, designed for oral administration, provides a delayed release of active ingredients suitable for the treatment of intestinal diseases in the colon, by means of a three-layer polymeric coating.

[0007] The PCT application No. WO 8,300,435 (Tillott JB Ltd.) discloses pharmaceutical compositions in capsule or tablet form for oral administration, useful for the treatment of intestinal diseases. Said compositions comprise a polymeric coating, thick enough to prevent their degradation before reaching the colon.

[0008] Therefore, the preparations known in the art provide an adequate drug release only when they are covered with multi-layer or very thick single-layer coatings; consequently drug release is not only "delayed", but also "controlled", over a very long period of time.

[0009] Therefore, the need for delayed-release oral pharmaceutical compositions overcoming the disadvantages of the aforesaid preparations is deeply felt.

Summary

[0010] The Applicant has now surprisingly found pharmaceutical compositions based on mesalazine or pharmaceutically acceptable salts thereof, suitable for oral administration in tablet form, containing a single-layer filming coating soluble at pH >7.0, which remains intact until it reaches the colon and prevents the drug release in the stomach and small intestine.

[0011] It is an object of the present invention to provide pharmaceutical compositions for oral administration in tablet form, containing mesalazine or pharmaceutically acceptable salts thereof as the active ingredient, comprising:

a) a nucleus comprising the active ingredient, and
b) a filming coating comprising a methacrylic acid/methyl acrylate/methyl methacrylate terpolymer.

[0012] The pharmaceutical compositions of the present invention are especially suitable for the treatment of inflammatory or irritative intestinal diseases.

[0013] Characteristics and advantages of the pharmaceutical compositions of the invention and of the relevant preparation process are illustrated in detail in the description reported below.

Brief description of the drawing

[0014] Fig. 1 shows the tablet release profile at pH 7.5, obtained by plotting the % amount of dissolved active ingredient *vs* time.

Detailed description of the invention

[0015] Nucleus a) may contain dispersing agents, preferably maltodextrin, which, compared with substances of the prior art exhibiting analogous dispersing properties, e.g. lactose and microcrystalline cellulose. is better tolerated by patients suffering from the aforementioned intestinal pathologies. In fact, said patients are often intolerant to lactose and must live on diets poor in fibre and cellulose.

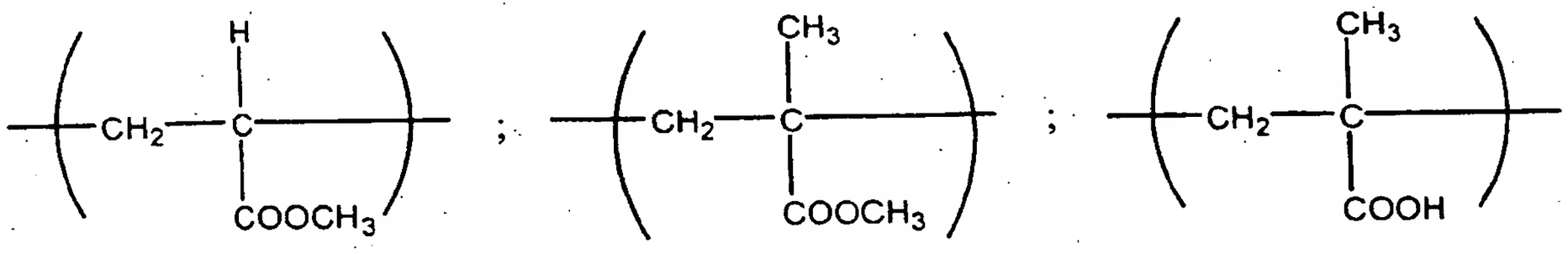
[0016] Typically, according to the present invention, the quantity of maltodextrin in nucleus a) is between 10% and 20% by wt., and more preferably 16% by wt., of the total weight of the active ingredient.

[0017] The composition of the nucleus according to the present invention may optionally contain further excipients selected out of binders, wetting agents, anticaking agents, lubricants and mixtures thereof.

[0018] Preferably, the binder is polyvinylpyrrolidone, the wetting agent is sodium lauryl sulphate, the anticaking agent is sodium starch glycolate, the lubricants are magnesium stearate, vegetable magnesium stearate, talc, and mixtures thereof.

[0019] In a preferred embodiment of the present composition, the total quantity of excipients is between 30% and 40% by wt. of the weight of the active ingredient.

[0020] According to the present invention, nucleus a) is coated with filming coating b) comprising an acrylic terpolymer, having the following repeating units in the chain:



[0021] Typically, the quantity of methyl acrylate monomeric unit is between 60% and 70% by wt., the quantity of methyl methacrylate is between 20% and 30% by wt., and the quantity of methacrylic acid is between 5% and 15% by wt. in respect of the total terpolymer weight.

[0022] The methyl acrylate/methyl methacrylate/methacrylic acid ratio is preferably equal to 65:25:10 by weight.

[0023] The filming coating of the invention is preferably prepared from a product available under the trademark Eudragit 4110 D ® from Rofarma Italia s.r.l., consisting of a 30% aqueous dispersion of the aforesaid methacrylic acid/methyl acrylate/methyl methacrylate terpolymer.

[0024] The quantity of acrylic terpolymer in the coating is preferably between 45% and 55% by wt., and more preferably between 49% and 50% by wt., of the total weight of the coating.

[0025] The filming coating of the invention may contain plasticising agents, and optionally lubricants, colouring agents, polishing agents and opacifying agents, too.

[0026] In a preferred embodiment, the plasticising agent is triethyl citrate, preferably in a 1:20 weight ratio to the acrylic terpolymer.

[0027] Typically, talc is used as lubricant for the present coating, red and yellow iron oxide are used as colouring agents, and titanium dioxide is used to increase the hiding power.

[0028] Polyethylene glycol 6000 is optionally used as a polishing agent of painted tablets.

[0029] The quantity of filming coating is preferably between 5.0% and 7.5% by wt. of the total weight of the nucleus. Its thickness is preferably lower than 60 μm, more preferably ranging from 25 to 50 μm, and most preferably equal to 30 μm.

[0030] The filming coating of the invention is completely insoluble at pH ≤ 6.0 and dissolves completely at pH >7.0.

[0031] It is a further object of the present invention to provide a process for the preparation of the aforesaid pharmaceutical compositions.

[0032] Said process comprises the following steps:

i) mixing the active ingredient with maltodextrin, wet granulating the resulting mixture with a solution containing binders and wetting agents, and drying the granular mass obtained;
ii) compressing the granular mass as obtained in step i), optionally added with excipients selected out of binders, wetting agents, anticaking agents, lubricants and mixtures thereof;
iii) adding a 30% aqueous dispersion of methacrylic acid/methyl acrylate/methyl methacrylate terpolymer with an NaOH aqueous solution until neutrality, then with the plasticising and polishing agents; optionally adding said dispersion with an aqueous suspension of colouring agents, optionally containing a lubricant and an opacifying

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agent, to give the aforementioned filming mixture;
iv) spray coating the tablets as obtained in step ii) above with the mixture prepared as described in step iii).

[0033] The compositions in tablet form being the object of the present invention contain the active ingredient in a quantity ranging from 200 to 800 mg. According to preferred embodiments, said tablets may contain 250, 400, 500, and 800 mg of the active ingredient.

[0034] The following example is conveyed by way of indication, not of limitation, of the present invention.

Example

[0035]

Composition of each tablet	
Active ingredient:	
5-aminosalicylic acid	400 mg
Excipients:	
maltodextrin	64 mg
polyvinylpyrrolidone	20 mg
sodium lauryl sulphate	4 mg
sodium starch glycolate	32 mg
talc	10 mg
magnesium stearate	8 mg
Coating:	
methyl acrylate/methyl methacrylate/methacrylic acid terpolymer	18 mg
sodium hydroxide	0.24 mg
triethyl citrate	0.9 mg
iron oxide red	3 mg
iron oxide yellow	0.5 mg
titanium dioxide	3 mg
talc	9 mg
polyethylene glycol 6000	1.8 mg

[0036] Mesalazine (22 kg) and maltodextrin (3.52 kg) were sieved through a vibrating screen and directly fed to a granulator, where they were added with a binding suspension (5.82 kg) previously prepared by mixing sodium lauryl sulphate (0.66 kg) and polyvinylpyrrolidone K 30 (3.3 kg) in pufiried water (13.5 kg), over a period of 1 hr.

[0037] The mixture of mesalazine with maltodextrin was blended with the binding suspension at 25° to 27°C for 2 min. Purified water (1 kg) was added and blending was continued.

[0038] The product obtained was forced through Quadro Comil's net, mod. Q 050/50. The resulting granular mass was dried at 50°C for 1.5 hr to a residual moisture content of 1.2% to 2.0%.

[0039] The granular mass was mixed with sodium starch glycolate (1.76 kg), talc (0.55 kg), and magnesium stearate (0.44 kg). The mixture obtained was compressed and formed into 55,000 tablets, each containing 400 mg mesalazine.

[0040] The filming coating was prepared as follows: Eudragit 4110 D ® (9.9 kg), as a 30% aqueous dispersion, was brought to neutrality by addition of a 1*N* NaOH solution (0.99 l) under gentle stirring, which stirring was continued for an additional ½ hr; then triethyl citrate (0.149 kg) and polyethylene glycol 6000 (Carbowax 6000) (0.99 kg) were added.

[0041] The resulting dispersion was slowly added with talc (1.485 kg), titanium dioxide (0.495 kg), iron oxide red (0.495 kg), and iron oxide yellow (0.085 kg), suspended in purified water (15 kg).

[0042] Considering that process losses equalled 10% approx., the quantity of paint obtained as described above was sufficient to coat 150,000 tablets.

[0043] Tablets prepared in advance were filmed by spraying said paint in a quantity adequate for covering each tablet with a 30 µm thick coating, equalling 6.73% by wt. of the weight of the nucleus.

Release tests

[0044] Although the compositions of the invention are coated with a single film layer, their release profile is unexpectedly better than that of mesalazine-based compositions of the prior art.

[0045] According to an *in vitro* test, the filming coating of the present invention does not dissolve even after 2 hrs at pH ≤ 6.0; at pH 7.0, it dissolves completely in an hour's time. At pH values of 6.5 to 7.0, the coating of the invention does not disintegrate in the first hour and disintegrates by 30% max. in the second hour.

[0046] The two *in vitro* release tests illustrated hereinbelow were conducted according to a U.S. Pharmacopoeia's (USP) dissolution test, on film-coated tablets of the invention prepared as described in the Example. In said tests, the active ingredient dosage was determined on a spectrophotometer (Beckman DU64) at 300 nm, provided with an automatic sampling system and a quartz cell with side of 0.2 cm.

Test No. 1

[0047] The active ingredient dosage in the dissolution medium was determined under the following operating conditions:

dissolution medium: simulated gastric fluid, pH 1.2
speed of rotation: 100 rpm
temperature: 37°C

[0048] At said pH value, no tablet disgregation took place even after 2 hrs.

[0049] This test provided evidence of the gastric resistance brought about by the coating of the invention, completely insoluble at acid pH.

Test No. 2

[0050] The active ingredient dosage was determined 30, 45, and 60 min after placing the tablet in a dissolution medium under the following conditions:

dissolution medium: buffer, pH 7.5
speed of rotation: 100 rpm
temperature: 37°C.

[0051] Test No. 2 was also conducted, under the same operating conditions, on mesalazine-based gastroresistant tablets of the prior art, in particular on tablets available under the trademark Asacol ® (800 mg) from Giuliani S.p.A.

[0052] The quantity of dissolved active ingredient measured at different times and expressed as % by wt. of the total weight of the tablet, is as follows:

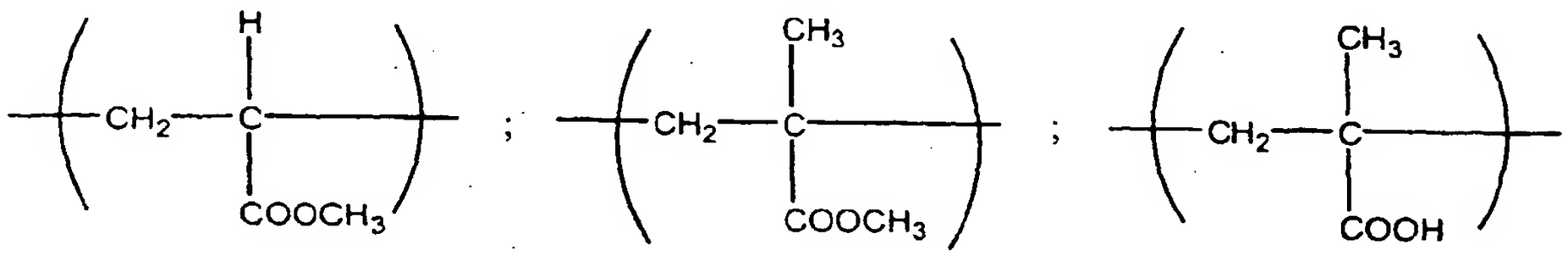
Time (min)	Active ingredient dissolved (%)	
	Asacol ®	Tablets of the invention
30	---	17.0
45	---	73.4
60	74.6	97.3
120	96.9	---

[0053] The release profile related to the coating of Asacol ® tablets (full line) and to the coating of tablets of the invention (broken line), respectively, is shown in Fig. 1. As may be seen, by comparing the two release profiles, the filming coating according to the present invention improves the active ingredient release at the pH value of the intestinal terminal portion: the tablets of the invention liberate almost the whole amount of drug after a one-hour residence at said pH, whereas the tablets of the prior art need two hours to achieve the same result.

Claims

1. Pharmaceutical compositions for oral administration in tablet form, containing mesalazine or pharmaceutically acceptable salts thereof, as the active ingredient, comprising:

   a) a nucleus comprising the active ingredient, and
   b) a filming coating containing as the sole filming polymer a terpolymer, having the following methyl acrylate, methyl methacrylate, methacrylic acid monomeric units in the chain:



2. The pharmaceutical compositions as claimed in claim 1 for the treatment of inflammatory or irritative intestinal diseases.

3. The pharmaceutical compositions as claimed in claim 1, wherein said nucleus a) comprises maltodextrin in a quantity between 10% and 20% by wt. of the total weight of the active ingredient.

4. The pharmaceutical compositions as claimed in claim 1, wherein said nucleus a) comprises excipients selected from the group consisting of binders, wetting agents, anticaking agents, lubricants and mixtures thereof.

5. The pharmaceutical compositions as claimed in claim 4, wherein the binder is polyvinylpyrrolidone, the wetting agent is sodium lauryl sulphate, the anticaking agent is sodium starch glycolate, the lubricants are magnesium stearate, vegetable magnesium stearate, talc, and mixtures thereof.

6. The pharmaceutical compositions as claimed in claim 1, wherein the total quantity of excipients in nucleus a) is between 30% and 40% by wt. of the weight of the active ingredient.

7. The pharmaceutical compositions as claimed in claim 1, wherein the quantity of said filming coating b) is between 5.0% and 7.5% by wt. of the total weight of the nucleus.

8. The pharmaceutical compositions as claimed in claim 1, wherein said filming coating b) has a thickness lower than of 60 μm.

9. The pharmaceutical compositions as claimed in claim 8, wherein said filming coating b) has a thickness ranging from 25 to 50 μm.

10. The pharmaceutical compositions as claimed in claim 8, wherein said filming coating b) has a thickness of 30 μm.

11. The pharmaceutical compositions as claimed in claim 1, wherein, in the terpolymer of filming coating b), the quantity of methyl acrylate is between 60% and 70% by wt., the quantity of methyl methacrylate is between 20% and 30% by wt., and the quantity of methacrylic acid is between 5% and 15% by wt. in respect of the total terpolymer weight.

12. The pharmaceutical compositions as claimed in claim 11, wherein the methyl acrylate/methyl methacrylate/methacrylic acid ratio by weight in said terpolymer is 65:25:10.

13. The pharmaceutical compositions as claimed in claim 1, wherein said filming coating a) contains excipients selected from the group consisting of plasticising, polishing, colouring, and opacifying agents and mixtures thereof.

14. The pharmaceutical compositions as claimed in claim 13, wherein said filming coating b) contains triethyl citrate as plasticising agent, polyethylene glycol 6000 as polishing agent, titanium dioxide as opacifying agent, talc as lubricant, while the colouring agents are selected from the group consisting of iron oxide red, iron oxide yellow,

and mixtures thereof.

15. The pharmaceutical compositions as claimed in claim 14, wherein said filming coating b) contains as the plasticising agent triethyl citrate in a 1:20 ratio by wt. to the methacrylic acid/methyl acrylate/methyl methacrylate terpolymer.

16. Process for the preparation of pharmaceutical compositions for oral administration in tablet form, containing mesalazine or pharmaceutically acceptable salts thereof as the active ingredient, comprising:

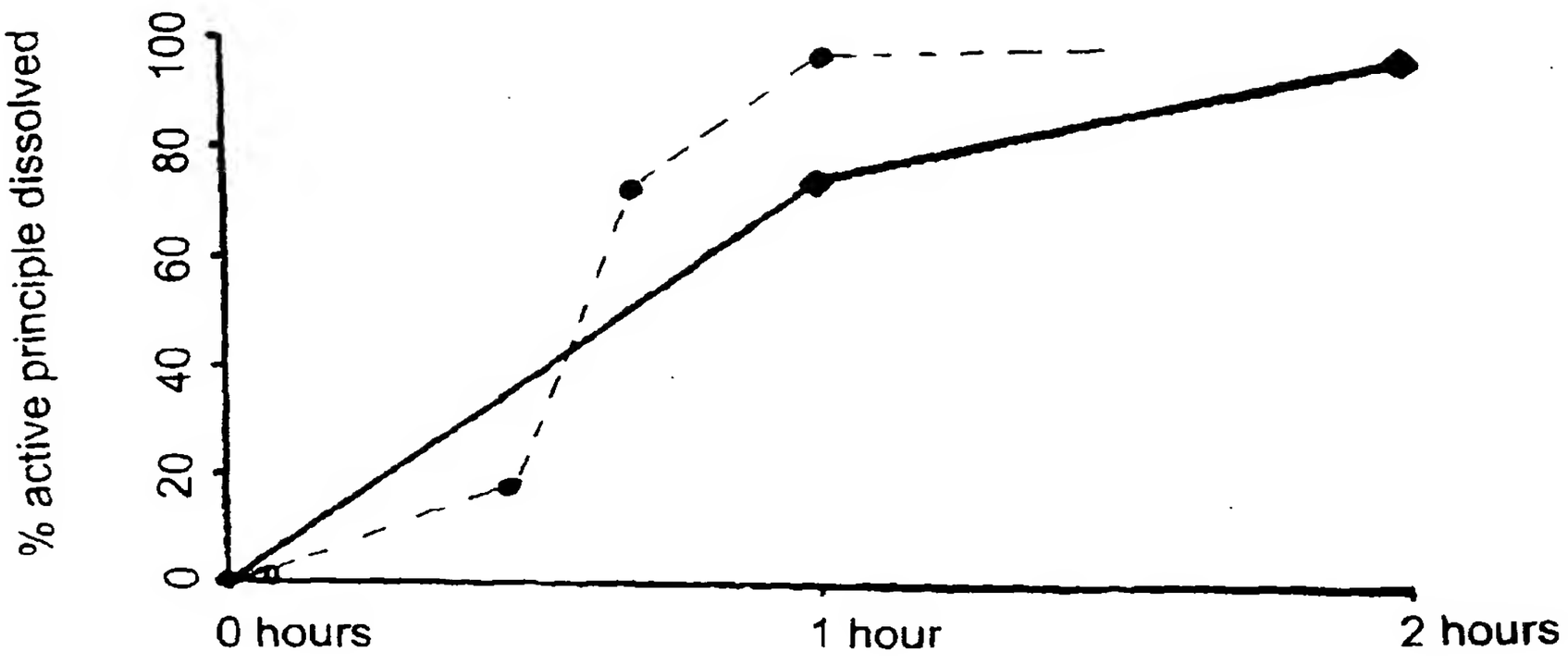
a) a nucleus comprising the active ingredient, and
b) a filming coating containing as the sole filming polymer a methyl acrylate/methyl methacrylate/methacrylic acid terpolymer,

said process comprising the following steps:

i) mixing the active ingredient with maltodextrin, wet granulating the resulting mixture with a solution containing binders and wetting agents, and drying the granular mass obtained;
ii) compressing the granular mass as obtained in step i), optionally added with excipients selected from the group consisting of binders, wetting agents, anticaking agents, lubricants and mixtures thereof;
iii) adding a 30% aqueous dispersion of methacrylic acid/methyl acrylate/methyl methacrylate terpolymer with the plasticising and polishing agent; optionally adding said dispersion with an aqueous suspension of colouring agents, optionally containing a lubricant and an opacifying agent, to give the aforementioned filming mixture;
iv) spray coating the tablets as obtained in step ii) above with the mixture prepared as described in step iii).

17. The process as claimed in claim 16, wherein the 30% aqueous dispersion of terpolymer as per step iii) is previously brought to neutrality by adding an NaOH aqueous solution.

Figure 1



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EUROPEAN SEARCH REPORT

Application Number
EP 99 12 2470

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Y	US 5 644 011 A (LEEHMANN KLAUS ET AL) 1 July 1997 (1997-07-01) * column 2, line 47 - line 65 * * column 5 - column 6; examples 1-4 * * claims 1,8,9,12,15,16,18-20 * ---	1,2,4-17	A61K9/20 A61K9/32 A61K31/606
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A	THE ROYAL PHARMACEUTICAL SOCIETY: "Martindale 31th edition" 1996 . JAMES EF REYNOLDS XP002131821 * page 1371 * -----	3	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	29 February 2000	Muller, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 12 2470

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